EXHIBIT 8

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Teratogenic Effects of Antiepileptic Drugs: Implications for the Management of Epilepsy in Women of Childbearing Age

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Summary: Exposure to antiepileptic drug (AED) treatment in utero occurs in 1 of every 250 newborns. The absolute risk of major malformations in these infants is about 7–10%, ~3–5% higher than in the general population. Specific risk factors include high maternal daily dosage or serum concentrations of AED, low folate levels, polytherapy, and generalized seizures during pregnancy. Adverse pregnancy outcomes, including congenital heart malformations, facial clefts, spina bifida aperta, hypospadias, growth retardation, and psychomotor and mental retardation, are associated with, although not necessarily caused by, AED exposure. Specific cognitive defects, hypertelorism, and nail hypoplasia can be causally related to specific AED exposures. To prevent teratogenic side effects, the prospective mother should be treated with AEDs only when absolutely necessary. Monotherapy with the AED that is most effective in the lowest possible daily dose (divided into at least two or three administrations) should be prescribed. High-dose folate supplementation (4–5 mg/day) reduces the risk of a neural tube defect in a child whose sibling had such a defect, but its impact on the specific teratogenic risks of AEDs is unknown. A substantial proportion of fetal malformations may be secondarily prevented by prenatal diagnosis, consisting of a fetal structural ultrasound examination at weeks 18 and 20 of gestation and, with VPA or CBZ administration, an α_1-fetoprotein analysis of amniotic fluid at week 16. Determination of a specific defect prevention strategy depends largely on parental attitudes toward prenatal diagnosis and termination of pregnancy, which should be discussed before conception. The availability of many new AEDs, many of which will be used in polytherapy, will make prospective evaluation of large numbers of pregnancy outcome on a population basis even more important in the future. **Key Words:** Anticonvulsants—Drug Toxicity—Teratogenicity—Folic acid—Prenatal diagnosis—Genetic counseling.

For women with epilepsy, pregnancy may present special complications. Almost every antiepileptic drug (AED) has been linked to teratogenic abnormalities in offspring. One fetus in every 250 is exposed to AEDs, and 1 newborn in every 5,000 in most countries is born with a major abnormality. The risk of major anomalies resulting from AED exposure is 3–5% greater than the 5% risk in the unexposed population. This figure is similar to that for the incidence in newborns of phenylketonuria or congenital hypothyrodism, maladies for which neonatal screening programs have been established in many countries.

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Can similar preventive measures be taken to reduce AED-induced teratogenesis? In general, a pregnant woman continues to receive an AED because the threat of seizures to her own health or life or that of her fetus outweighs any risk of teratogenic effects. However, there are many instances in which AED exposure could have been avoided, such as when contraceptive measures fail or when a woman of childbearing age has not been properly informed of the potential teratogenic effects of the AED she is taking. We must explore how these opportunities for prevention can be effectively employed.

Can we hope to see the development of AEDs with fewer or no teratogenic effects? In the near future this seems unlikely. Among the many new AEDs awaiting approval for clinical use, some, such as topiramate and vigabatrin, displayed tera-

togenic effects in the first animal models in which they were tested, before they were studied in clinical trials. In the short run, the medical community should focus on developing better strategies to monitor the safety of new AEDs in women of childbearing age.

TERATOGENIC EFFECTS OF AEDs

Primarily physical malformations

Significant teratogenic effects have been found to accompany administration of all major AEDs. At present, carbamazepine (CBZ) and valproate (VPA), which were introduced some 10–25 years ago, are believed to be as teratogenic as the older AEDs, phenobarbital (PB), phenytoin (PHT), and primidone (PRM). However, very different malformations have been observed in these two groups.

PB, PHT, and PRM have been linked to congenital heart defects, cleft lip and cleft palate and, less often, skeletal defects and closure defects of the neural tube (Lindhout et al., 1992*a*). Fetal syndromes involving multiple dysmorphic features (Hanson, 1986), especially hypertelorism and nail hypoplasia (Gailey et al., 1988*a*), with or without mental deficiency, have also been associated with these AEDs.

Spina bifida aperta and hypospadias have been associated with exposure to VPA and, to a lesser extent, CBZ (Lindhout et al., 1992*a*). In pregnant women receiving VPA, the risk of spina bifida aperta in the fetus is approximately 1–2%; this figure may be somewhat increased with monotherapy and somewhat reduced with polytherapy (Omtzigt et al., 1992*a*). In women receiving CBZ, the risk is about 0.5–1% (Rosa, 1991), whereas the risk is only 0.3–0.4% for those receiving PHT and/or barbiturates. Surprisingly, in prospective studies of VPA, only one newborn exposed to VPA in utero had anencephaly (Lindhout and Schmidt, 1986). At present, it is unclear whether the risk of fetal hydrocephaly or anencephaly is increased in pregnant women receiving CBZ.

The experience with CBZ and VPA provides important lessons regarding the risks of teratogenesis due to AEDs. Introduced in The Netherlands in 1968 and 1971, respectively, CBZ and VPA are now each prescribed to more than 30% of adults with epilepsy, including pregnant women. Although these AEDs were well tolerated in animals during preclinical testing, subsequently they were found to be teratogenic to the human fetus. Failure to detect these effects in early clinical trials was probably due to the small number of pregnancies evaluated and the confounding effects of co-medication. Additional prospective studies are ongoing.

Growth, mental, and psychomotor development

Some 20 years ago, maternal AED use was believed to increase significantly the risk of mental or psychomotor retardation in offspring (Hanson, 1986). However, the accuracy of that observation has been consistently questioned and challenged, although not entirely discredited. In many cases, the children observed in the 1970s had multiple dysmorphic features and anomalies, often including mental retardation, and had been selectively referred for syndrome diagnosis. The dysmorphologists involved in these cases were able to describe the extreme expression of the various fetal AED syndromes; however, they were not able to prove conclusively that the mental or growth retardation often observed with these syndromes was causally linked to AED exposure in utero and are not associated with genetic factors related or unrelated to the maternal epilepsy.

Prospective studies that controlled for a variety of parameters, including socioeconomic factors, failed to confirm a high risk for general mental deficiency among children exposed prenatally to AEDs (Gailey et al., 1988*b*). These studies noted that such children were at higher risk for developing specific isolated cognitive defects than for developing aspecific mental retardation. However, it was unclear whether this risk of cognitive defects was due to fetal exposure to maternal seizures, to genetic factors related to the maternal epileptic disease, or to paternal factors stemming from limitations in choice of partners for women with epilepsy compared with women in the general population (Gailey et al., 1990).

Although the findings of these prospective studies appear to contradict earlier studies, it must be remembered that the studies differed not only in design but also in time frame, during which prescription patterns varied. Judging from the many initial case reports and from our own retrospective analyses, fetal AED syndrome typically has occurred after prenatal exposure to a combination of barbiturates, especially the combination of PB plus PRM plus PHT. Prospective studies have significantly lowered the estimated frequency of the extreme expression of fetal AED syndromes but have failed to disprove their existence. The impact of contributing factors, including high AED dosages, specific AED combinations, and an infrequent genetic susceptibility to teratogenic agents, must be studied in larger trials.

When controlled for socioeconomic factors and parental findings, the same prospective studies reported that only hypertelorism and nail hypoplasia are causally linked to prenatal AED exposure. All

other dysmorphic features either were observed with equal frequency in AED-exposed children and controls or could be explained by parental findings (Gailey et al., 1988*a*). Moreover, nail hypoplasia tends to resolve during childhood, and in most cases is followed by normal nail growth.

Maternal AED administration has also been associated with various degrees of prenatal and postnatal growth retardation. Recent controlled prospective studies, however, showed that any growth difference between AED-exposed and control children is small and usually disappears at follow-up examinations by the age of 5.5 years (Gailey and Granström, 1989).

IMPACT OF DOSAGE ON TERATOGENIC RISK

Results of animal experiments have often suggested a correlation between higher dosages of AEDs and increased teratogenic risks. Such an association has not yet been conclusively found in human subjects, with the exception of VPA-induced spina bifida, probably because only a small number of pregnancies have been evaluated prospectively and controlled for all possible confounding factors.

The most relevant studies in this area have focused on VPA dosage and teratogenicity. A significant relation between the incidence of spina bifida and the total daily dosage or dose per administration of VPA was recently noted in a prospective cohort of 297 pregnancies with fetal exposure to AEDs. In six cases of spina bifida (including one concordantly affected monozygotic twin pair), the average daily dosage of VPA received by the mothers was 1,640 mg; among 83 VPA-exposed pregnancies with normal outcome, the average daily dosage was 950 mg ($p < 0.001$) (Omtzigt et al., 1992*a*). Whereas both the total daily dose of VPA and the dose per administration correlated with spina bifida outcome, the number of administrations per day did not (Omtzigt et al., 1992*a*). An additional 16 cases of VPA-associated neural tube defects (NTDs) in The Netherlands are known to the authors. In these cases, the maternal daily dose of VPA was 1,470 mg (Lindhout et al., 1992*b*), within the same dosage range as in the cases of spina bifida. This supports a likely correlation between dosage and effect. Whether the maternal daily dosage or the dose per administration influences the teratogenic effects of VPA on the developing human neural tube is at present unclear. The higher the dose per administration, the higher the peak levels in human serum. Animal experiments in which constant infusions of VPA were compared with repeated single injections clearly showed that the incidence of NTDs correlated not with total daily dosage but with peak levels connected with dose per administration (Nau, 1985).

As a result of these findings in animal models and human subjects, recommendations have been developed for VPA administration in women with epilepsy who are planning to conceive. When VPA is necessary, the total daily dosage should be divided into at least three administrations per day, and a reduction in the dose per administration. This also results in a reduction of the total daily dosage. However, because dose is only a relative risk factor, these measures will not prevent all cases of VPA-induced spina bifida. Normal infants have been born to women who received VPA in dosages exceeding 2,400 mg/day, but spina bifida has occurred when maternal dosage was only 600 mg VPA/day (Lindhout et al., 1992*b*).

TERATOGENIC RISKS POSED BY AED COMBINATIONS

Several studies have demonstrated an increased risk for birth defects in infants exposed to AED combinations in utero. Risk has been correlated with number of AEDs, specific combinations, and a quantitative parameter of overall AED exposure that considered the number of AEDs as well as the relative daily dosage of each drug (Nakane et al., 1980; Lindhout et al., 1982; Kaneko et al., 1984; Miyakoshi and Seino, 1984). The combinations of PB plus PHT plus PRM (Dansky, 1989) and CBZ plus PB plus VPA with or without PHT (Lindhout et al., 1982) are associated with high teratogenic risk and should be avoided in women who may want to become pregnant. The increased risks posed by these combinations probably occur as a consequence of the metabolic interactions of these AEDs, which yield an accumulation of potentially teratogenic intermediate metabolites that have not yet been identified. With the CBZ combination, the teratogenic effect is probably caused by one of the various epoxides of CBZ or of any of the other AEDs in that combination (Lindhout et al., 1984).

The combination of CBZ plus PB plus VPA, with or without PHT, causes hyponatremia in about 10–15% of adult patients. The embryotoxic effects of patients' sera on rat embryos is correlated with the degree of hyponatremia (Lindhout et al., 1987). Hyponatremia occurs even more frequently with oxcarbazepine (OCBZ), marketed recently in The Netherlands, than with CBZ. It is unclear whether this side effect represents the teratogenic mechanism or only a parallel phenomenon. It appears pru-

dent, nevertheless, to consider substituting OCBZ for another AED in women desiring to become pregnant who have a hyponatremic reaction to OCBZ. If OCBZ is continued, monitoring of both the sodium level and the OCBZ level during pregnancy may aid in evaluation of the significance of sodium levels in abnormal pregnancy outcome.

AED polytherapy does not always increase the risk for birth defects. In fact, it may lower or eliminate that risk in some instances, as when metabolic interactions of a specific AED combination yield lower concentrations of the ultimate teratogenic agent than those produced by monotherapy. This may explain the somewhat lower risk for NTDs when VPA is administered in combination with PB, which appears to lower VPA levels by induction of VPA metabolism (Nau, 1986).

GENETIC PREDISPOSITION TO AED-INDUCED TERATOGENESIS

In addition to the potential direct effect of AED dose and combinations on teratogenesis, other factors may co-determine whether AED exposure is teratogenic, including maternal nutrition, maternal and fetal biologic factors, and maternal and paternal genetic factors. Birth defects in newborns prenatally exposed to AEDs tend to cluster in the same family to a greater extent than can be explained by the general risk facing AED-exposed fetuses; when an infant has been exposed in utero to an AED and shows a birth defect known to be associated with that particular AED, the risk for a birth defect in a subsequent prenatally exposed sibling is greater than the average risk of malformation associated with that AED. Two pairs of monozygotic twins were described who were concordant for spina bifida (Robert et al., 1984; Lindhout et al., 1992*b*), whereas the concordancy rate for spina bifida in the general population of twins, even monozygotic twins, does not exceed 10–15% (Elwood et al., 1992). The concept of individual genetic variations in susceptibility to a teratogen is supported by the fact that discordancy for AED-induced or -associated birth defects has been described only in dizygotic twins and heteropaternal twins. To fully assess the impact of predisposing genetic factors, analysis of large numbers of siblings with equal maternal exposure and of mono- and dizygotic twins will be required.

The nature of genetic predisposing factors is still unclear. Pharmacogenetic differences among offspring of different mothers, as well as among offspring of the same mother, are probably involved. In a group of children whose mothers with epilepsy had received PHT during pregnancy, the lymphocytes of children with major PHT-induced malformations were more sensitive to toxic PHT metabolites grown in vitro than were lymphocytes from children without these defects. The investigators concluded that the lymphocytes of the infants with PHT-associated birth defects were probably deficient in the ability to detoxify toxic metabolites and that this deficiency was genetically determined. The same deficiency was observed in one of the two parents, either the mother or the father (Strickler et al., 1985). Therefore, this putative genetic factor is not necessarily linked to the maternal epilepsy.

Epoxide hydratase is one of the enzymes involved in the detoxification of AEDs. Recently, similar differences between normal and affected offspring exposed to PHT in utero were found in the epoxide hydratase activity of cultured fibroblasts and amniotic fluid cells (Buehler et al., 1990). Although these findings again suggest a role for genetic predisposing factors, they should be put into proper perspective. Both studies demonstrated differences between groups of exposed children, but overlap in results between groups did not allow any interpretation or prediction concerning individuals. In addition, the types of defects associated with the measured activity were different in the two studies. The lymphocyte sensitivity measured in the first study (Strickler et al., 1985) correlated with major malformations but not with a large number of dysmorphic features examined in a standardized manner. The epoxide hydratase activity measured in the second study (Buehler et al., 1990) correlated with the presence or absence of the fetal hydantoin syndrome, which is characterized primarily by dysmorphic features and for which the presence of a major anomaly is not obligatory. In addition, in the latter study, dysmorphic features, the diagnosis of which is notoriously sensitive to subjective interpretation and experience, were not evaluated in a standardized manner. The study also provided no data on the parental levels of epoxide hydratase, leaving open the question of whether the lower levels observed in the affected offspring were genetically determined and predisposing to the teratogenic effects or were secondary to AED exposure, for example.

Genetic factors may play a role independent of drug metabolism. It is noteworthy that 25% of infants who have spina bifida that correlates with maternal AED administration also have a positive family history for NTDs. To reduce differences in recall bias, such family histories should be compared not with those of healthy controls but with those of cases of spina bifida not associated with maternal AED administration, matched for type of defect and

method of diagnosis (pre- or postnatal). Although such a study has not yet been performed, it is clear that in the Dutch cases of VPA-associated spina bifida, the family histories of both parents are equally positive for NTDs (Lindhout et al., 1992*b*). From this, a strong argument can be made against the hypothesis that the maternal epilepsy gene causes or predisposes to the NTDs associated with maternal VPA administration. Genetic predisposing factors appear to operate independent of the maternal epileptic genotype.

FOLIC ACID SUPPLEMENTATION IN PREVENTION OF AED-INDUCED BIRTH DEFECTS

Folic acid and "spontaneous" NTDs

The effect of folic acid (FA) administration on recurrence of NTDs has been studied extensively. Only recently, however, has a well-controlled prospective trial yielded specific results: In women who have given birth to a child with an NTD, periconceptional supplementation with FA at a pharmacologic dose of 4 mg/day reduces the risk of recurrence of NTDs in subsequent children from 3.5 to 0.7%, without producing adverse fetal effects (Medical Research Council, 1991). This finding has prompted the universal recommendation that any woman who has had a child with NTDs begin high-dose FA supplementation at least 1 month in advance of a subsequent planned pregnancy, irrespective of her nutritional status, to be continued until the third month of pregnancy. It is unknown whether FA supplementation is effective in populations with a lower background prevalence of NTDs and lower recurrence risks. It is also unclear to what extent FA, at the pharmacologic dosage of 4 mg/day, exerts its activity by correcting an unknown maternal or fetal genetic defect or by correcting a nutritional deficiency.

High-dose FA supplementation and AED-induced teratogenesis

Periconceptual FA supplementation is often recommended as a safe way for all women receiving AEDs to reduce teratogenic risk, especially those women receiving VPA and CBZ, which are associated with an increased risk for NTDs. This recommendation is based on the demonstrated relationship between maternal FA status and any adverse pregnancy outcome, including spontaneous abortions, in women receiving AEDs (Dansky, 1989). However, this may be a dangerous assumption, for several reasons.

First, it is unknown whether the teratogenicity of AEDs is derived through their interference with FA-related pathways. AED treatment may aggravate the physiologic decrease in FA levels associated with pregnancy. However, PHT and barbiturates, the AEDs that induce the most marked changes in FA status, pose the lowest risk for fetal NTDs. Conversely, VPA and CBZ, the AEDs that are particularly associated with spina bifida, have a much lesser influence on measured FA parameters. AED treatment in general may be associated with changes in many unmonitored physiologic parameters other than FA levels. Therefore, the observation of an adverse outcome when only one of these parameters (i.e., FA) is evaluated does not in itself prove that the association is of pathogenetic significance but may merely reflect an association with the level of the AED, its metabolites, or any of the many other physiologic parameters that may be altered by medication.

In animal experiments, the teratogenic action of VPA was potentiated by FA deficiency and was reduced in nutritionally normal dams by folinic acid supplementation (Trotz et al., 1987). This partially protective effect of folinic acid could not be reproduced by others, perhaps in part because of diurnal fluctuations in FA metabolism (Wegner and Nau, 1991). In vitro studies provided some evidence for a specific inhibition by VPA of the enzyme glutamate formyl transferase. This finding is consistent with the protective effect of folinic acid, the product of the inhibited pathway; when folinic acid is administered as a supplement, the metabolic block is bypassed (Wegner and Nau, 1992).

In summary, clinical–epidemiologic studies offer no proof that FA deficiency is by itself the pathogenetic mechanism for AED-induced teratogenesis, nor that FA supplementation with pharmacologic doses is protective. Although high-dose FA supplementation is regarded as safe when applied in cases of recurrence risk, its safety in women receiving AEDs is equivocal. Therefore, high-dose FA supplementation should be reserved only for those women receiving AEDs who wish to become pregnant and who have signs of FA deficiency. Furthermore, women with vitamin B_{12} deficiency should not be treated with high-dose FA supplementation until they have been treated for the deficiency, to avoid the complication of subacute combined degeneration of the posterior and lateral columns of the spinal cord.

The decision to treat all women receiving AEDs with pharmacologic doses of FA (4–5 mg) must be withheld until there is clear evidence from animal experiments and controlled clinical trials to demonstrate that such treatment is effective and without untoward effects. Given the relatively high and spe-

cific risk for spina bifida with maternal VPA administration and the preliminary animal experimental data about the possible pathogenetic background, the most rational approach would be to set up a clinical trial with folinic acid rather than FA (or with FA as a second control in addition to a placebo control), provided that pilot studies do not demonstrate loss of seizure control by the high-dose FA or folinic acid treatment.

Low-dose FA supplementation in maternal AED treatment

In a recent Hungarian population-based, randomized, double-blind, controlled study in healthy pregnant women, without any known increased risk of having a fetus with NTDs, the effect of a multivitamin preparation containing a low dose of FA (0.8 mg/day) on birth defects was compared with that of a mineral preparation with a low dose of vitamin C only. A significant reduction in the incidence of NTDs (0/2,052 vs. 6/2,104) was reported among pregnant women who took multivitamins with FA (Czeizel and Dudás, 1992). Previous retrospective or uncontrolled studies employing lower daily doses of FA (0.1–0.4 or 0.5 mg) had shown similar effects. Recognizing the need to improve the FA status of women of childbearing age, health authorities from the United States, United Kingdom and The Netherlands now recommend the availability of a low-dose FA pill, promotion of a FA-rich diet, fortification of selected food staples, or a combination of these. The measures to be taken depend on the food and vitamin consumption pattern of the target population of interest, which may be increasingly diverse with regard to ethnic variation. Daily supplementation with a low dose of FA (0.4 mg/day) is advised for all women of childbearing age when food fortification is not immediately feasible. There appears to be no reason to withhold this low-dose FA from women receiving AEDs, except in cases of symptomatic FA deficiency or recurrence risk for NTDs, when higher doses should be given.

PRENATAL DIAGNOSIS OF BIRTH DEFECTS

Spina bifida aperta can be diagnosed prenatally by α_1-fetoprotein (AFP) analysis of amniotic fluid obtained between weeks 16 and 20 of gestation. AFP analysis is usually offered to pregnant women in a high-risk category, e.g., if a previous child has been born with an NTD or if a sibling of one of the parents has such a defect. Because the risk of spina bifida has been shown to be about equally high when the mother is receiving VPA or CBZ (1–2% and 0.5–1%, respectively), prenatal diagnosis should also be offered to those women. AFP analysis of amniotic fluid was demonstrated to reliat allow prenatal diagnosis of VPA-induced spina fida in five pregnancies with six affected fetus (one monozygotic twin concordant for the defe (Omtzigt et al., 1992*a*); however the reliability AFP screening of maternal serum in detecting VP induced spina bifida has been questioned (Omtzi et al., 1992*b*). The risk for NTDs associated wi other AEDs is about 0.3–0.4%, slightly higher th the risk in the general population in most countrie Whether amniotic fluid analysis is offered to wom receiving these AEDs depends heavily on local s uations and health care policies.

Structural ultrasound examination of the fet may help to detect some of the other major malfo mations associated with AED exposure. Ideally, should be performed between weeks 18 and 20 gestation (Wladimiroff et al., 1988). The results ma be helpful in optimizing obstetric and perinatal ca or in deciding whether to terminate pregnanc However, the limitations of prenatal ultrasoun should be fully explained to the parents. Not a defects, whether AED-induced or not, can be dia nosed prenatally. When a malformation is found, prognosis cannot always be given and additional a normalities, including mental deficiency, may r main masked until after birth.

If lethal or untreatable defects are diagnose some parents may decide to abort the fetus. In prospective series of more than 350 prenatal diag noses of AED-exposed fetuses by AFP-analysis o amniotic fluid and structural ultrasound in Th Netherlands, eight pregnancies were terminated be cause of spina bifida (seven fetuses, including on monozygotic twin pair, exposed to VPA and, in on instance, to VPA plus CBZ), and one pregnanc was aborted because of severe hydrocephaly (at tributed to CBZ) (Omtzigt et al., 1992*a*, update through July 15, 1992).

Transvaginal ultrasound examination may help t identify severe AED-associated anomalies as earl as the first trimester of pregnancy. The possibilit of detecting and aborting malformed fetuses at th early stages may spare many parents the emotion ally difficult decision of whether to abort a preg nancy in the late stages, after malformations have been diagnosed through amniotic fluid analysis o transabdominal ultrasound examination.

Late-term abortions may also pose physical health risks for the mother. Women with epilepsy receiving AEDs may be at much greater risk for developing seizures or status epilepticus during late termination of pregnancy by prostaglandin injection (Brandenburg et al., 1990). It is unclear whether the prostaglandin alone is responsible for this increased

risk. The seizure threshold may be lowered as a result of maternal stress and/or sleeping disturbances experienced on learning about the adverse prenatal diagnosis. Moreover, there may be an increased risk for noncompliance with an AED treatment regimen during the period between the woman's notification of diagnosis and termination of the pregnancy (Omtzigt et al., 1992*c*). Therefore, the physician is well advised to emphasize the need for continued AED therapy despite a woman's grief that her medication is the most likely cause of the fetal malformation. Medication should be monitored closely during the days preceding and after the abortion procedure.

RECURRENCE RISK FOR AED-INDUCED BIRTH DEFECTS AND EPILEPSY

Pediatric, dysmorphologic, and clinical genetic analyses are indicated for any malformation or retardation that occurs after prenatal exposure to AEDs. All causes other than the AED exposure must be ruled out. The results can help to determine the recurrence risk and the options for prevention, primarily by adjustment of therapy and secondarily by prenatal diagnosis and possible termination of pregnancy.

Patients should also be educated about the recurrence risk for epilepsy; in many cases, a clinical genetic workup may be required. A discussion of this issue, however, is beyond the scope of this article.

FUTURE PROSPECTS FOR NEW AEDs

In the search for AEDs with greater efficacy against seizures and with fewer adverse effects, many new antiepileptic agents have been developed in the past decade. The marketing of these agents presents a dramatically new situation for clinicians.

Of the many new AEDs, including lamotrigine, felbamate, gabapentin, vigabatrin (VGB), OCBZ, loreclezole, losigamone, tiagabine, ralitoline, and fosphenytoin, at least four have been released for prescription in one or more Western countries. Many other AED compounds, including topiramate (TPM), stiripentol, and zonisamide, are being studied in ongoing clinical trials. The simultaneous availability of a large number of new AEDs carries with it a potentially new sociomedical side effect of drug development.

Most clinical trials of new AEDs have a design in which the new compound is tested as add-on medication. This implies that, upon release for general prescription, most experience of a new drug with respect to efficacy comes from its use in polytherapy. Indeed, some patients can be treated effectively only by a combination of AEDs, usually discovered empirically, not rationally, but most patients do *not* need it. Let us first wait for each of these new compounds to prove its therapeutic place in the forthcoming years. The therapeutic value of newly approved AEDs should be proven conclusively before clinicians begin to suggest a rational basis for combining them with each other.

This approach is especially relevant to the treatment of epilepsy in women of childbearing age. It is already difficult to extrapolate the teratogenic risks of single compounds from animal species to humans; for polytherapy this is virtually impossible, particularly because no institution will take responsibility for testing the teratogenicity of "rational drug combinations" in animal species. Polytherapy, especially when not absolutely required for seizure control, implies taking more risks than necessary.

PREGNANCY EXPERIENCE WITH VGB AND OCBZ

Recently, VGB and OCBZ were introduced in The Netherlands and in several other European countries. At the two highest doses tested, VGB induced cleft palate in the offspring of New Zealand White rabbits. Whether OCBZ is a safe alternative to CBZ, despite the higher frequency of hyponatremia, can only become clear during clinical practice. Friis (1993) reported the outcomes of 12 pregnancies in women receiving OCBZ: Three ended in spontaneous miscarriage and nine ended with the birth of a healthy baby. Table 1 summarizes known pregnancy outcomes in women receiving VGB or OCBZ in The Netherlands. The numbers are too small and the factors too many to support any conclusions with respect to safety or risks of these compounds.

In a series of 11 prospectively monitored pregnancies where the mothers received OCBZ, one major malformation, spina bifida aperta, was diagnosed prenatally in a woman receiving 3,000 mg OCBZ/day; this was followed by termination of pregnancy. However, the woman also had received clobazam (CLB) and VPA (1,800 mg/day). A previous child from the same couple had no major malformations, although it had been exposed prenatally to a combination of CLB, VPA in the same dosage, and a 10% lower daily dosage of OCBZ (2,700 mg). A third child of this couple also was normal after a pregnancy during which the mother had received daily 3,000 mg OCBZ and CLB but no VPA. No conclusion can be drawn concerning the potential contribution of OCBZ to the NTD in the second

TABLE 1. *Pregnancies outcome with oxcarbazepine and with vigabatrin*

Case no.	Parental epilepsy	OCBZ	VGB	CBZ	VPA	PHT	CLZ	CLB	AZM	FA	OCF	Child
Prospective pregnancies with OCBZ[a]												
1	♀	500	—	400	—	—	—	—	2	—	—	Normal
2	♀	1,350	—	—	—	325	—	—	—	+	—	Normal
3*	♀	2,700	—	—	1,800	—	—	+	—	—	—	} Normal
	♂	—	—	—	—	600	30	—	—	—	—	
4*	♀	3,000	—	—	1,800	—	—	30	—	—	—	} SBA, (TOP)
	♂	—	—	—	—	600	30	—	—	—	—	
5*	♀	3,000	—	—	—	—	—	30	—	—	—	} Normal
	♂	—	—	—	—	600	30	—	—	—	—	
6	♀	1,650	—	—	800	—	—	—	—	—	—	Normal
7	♀	750	—	—	900	—	—	—	—	—	—	Normal (Thyrax[b])
8	♀	900	—	—	—	—	—	—	—	—	—	"Inhibition weakness"
9	♀	900	—	—	—	—	—	—	—	—	—	?
10	♀	1,050	—	—	—	—	—	—	—	—	—	Eyelid edema feeding problem disproportion head ↔ trunk
11	♀	1,500	—	—	—	—	—	—	—	—	—	Normal
Prospective pregnancy with VGB[a]												
12	♀	1,500	3,500	—	—	—	—	—	—	—	—	Hypospadias
Retrospectively ascertained case with defect after OCBZ												
13	♀	+	—	—	—	—	—	—	—	—	+	Terminal transverse defect (3 fingers)

OCBZ, oxcarbazepine; CBZ, carbamazepine; VPA, valproate; PHT, phenytoin; CLZ, clorazepate; CLB, clobazam; AZM, acetazolamide; FA, folic acid; OCF, oral contraceptive failure; VGB, vigabatrin; SBA, spina bifida apertas; TOP, termination of pregnancy.
♀, maternal epilepsy; ♂, paternal epilepsy; +, positive.
* Subsequent pregnancies of the same woman.
[a] Dosages, mg/day.
[b] Maternal Thyrax therapy.

pregnancy of this woman. Her husband also had epilepsy treated with PHT and clorazepate, the latter of which has no known association with NTDs in offspring of male epileptic patients on medication.

Several pregnancies in women receiving VGB in The Netherlands are being evaluated. The first pregnancy outcome with VGB use was obtained from a prospective cohort study. It was the mother's fourth pregnancy. A boy was born with coronal hypospadias, broad depressed nasal bridge, telecanthus, high-arched palate, prominent ear shelves and lobes, upward slant of palpebral fissures, apparently small palpebral fissures, diastasis musculus recti abdominis, slightly capitonated deep palmar flexion creases, bilateral clinodactyly of fourth toes, and apparently wide internipple distance (see Table 1, patient no. 12). The mother had received 3,500 mg VGB daily in the beginning of pregnancy; this dosage was lowered during pregnancy to 1,500–2,000 mg and increased again toward the end of pregnancy. In addition, she had received 800 mg CBZ throughout pregnancy. However, the previous three pregnancies of the same woman complicate interpretation of this fourth pregnancy. In her first pregnancy, which resulted from oral contraceptive failure, she received PHT for the first 4 weeks, after which she was switched to CBZ until term. At birth, this first child also showed coronal hypospadias. The second pregnancy, in which she had received CBZ (1,000 mg/day), ended in a miscarriage. The third pregnancy, with the same daily dosage of CBZ, resulted in the birth of a healthy boy. A dysmorphologic examination provided no clue as to the cause of the hypospadias in two children of this mother. The diagnosis of Opitz syndrome was considered but rejected. The findings of earlier studies suggest that prenatal exposure to CBZ is associated with hypospadias, and CBZ may have caused the hypospadias in the most recent pregnancy, in view of the embryonic period in which the male urethra closes. On the other hand, it cannot be ruled out that VGB played a role in the occurrence of this defect and of the dysmorphic features. Whether there is a VGB-specific fetal syndrome can be determined only by evaluation of larger numbers of prospectively monitored pregnancies. It is noteworthy that VGB induces clefts in the New Zealand White rabbit and that diaphragmatic hernia, which is also representative of a fusion defect, has been observed in a human pregnancy after maternal VGB use (Krämer, 1992). A third alternative is that the hypospadias in two of the three children is of genetic origin and has nothing to do with the maternal AED.

These case reports also illustrate how a clinical

genetic workup can be used to account for the results of all pregnancies by identifying the same or different medications administered during each pregnancy, the dysmorphologic findings in the family, and the family history. This is more fruitful than merely listing AED exposures and pregnancy outcomes and calculating drug-specific frequencies of birth defects.

STRATEGIES FOR PREVENTING AED-INDUCED TERATOGENESIS

The general policy with regard to the prescription of new drugs during pregnancy for chronic disorders such as epilepsy is far from clear. Inserts to AED packages usually state that pregnancy is contraindicated while receiving the medication, or that treatment with the drug is contraindicated during pregnancy, implicitly releasing the manufacturer from responsibility for any adverse outcome after exposure. Nevertheless, if a new AED eventually is determined to be the single AED effective in a particular group of epilepsy patients, they probably will continue receiving that medication during pregnancy despite advice to the contrary from their doctor or from the package insert. Most often, these aspects of treatment are discussed rather infrequently, or not at all, with the patient when pregnancy is not at issue. Therefore, it is not unusual for the patient with epilepsy or her doctor to express concerns about the safety of AEDs only after the patient is pregnant and important periods of embryogenesis have already passed. Furthermore, manufacturers are reluctant to set up postmarketing surveillance studies of pregnancy outcome, as involvement in such a study would imply that the manufacturer is deliberately exposing human fetuses to a possible teratogenic agent. As a result, much valuable information that could be gathered about pregnancy outcomes after exposure to specific new AEDs is lost.

The current situation delays both the identification of specific teratogenic effects of new AEDs and implementation of appropriate preventive measures. To find solutions, constructive discussions must take place among manufacturers and professional and lay organizations. A rational approach includes two steps. (1) Evaluate the therapeutic value of a new AED after a significant period of availability in private practice, e.g., 5 years. During this time, prescriptions to women of childbearing age should be avoided. (2) If and when an AED clearly shows unique therapeutic properties in specific epileptic conditions vis-à-vis other currently available AEDs, therapy with the AED may be considered in women of childbearing age with similar conditions, provided that measures have been taken to evaluate the outcome of all pregnancies.

Special caution should be taken when treatment is considered with new AEDs that have exhibited teratogenic activity in animals, e.g., VGB (discussed above) and TPM. TPM induced malformations (digital defects, clefts) in mice at all three doses tested and in rats at the two highest doses tested, and was fetotoxic in the rabbit (Kramer, 1993, unpublished data). The development and marketing of such teratogenic drugs are often justified on the grounds that the defects observed are no more severe than those observed with presently available AEDs. However, such a comparison neglects the fact that, after the discovery of human teratogenicity of the currently available AEDs, higher doses had to be tested in many different animal species and strains before the appropriate animal model reflecting the human malformation pattern was found. VGB and TPM, on the other hand, already have displayed similar teratogenic activity in the first animal species tested. Therefore, the proposed two-step approach is even more relevant to these compounds. Only when a drug's therapeutic uniqueness has been proven in other patients can prescription to women of childbearing age be considered, and only when full information about the drug's potential teratogenicity is provided to the patient and evaluation of the outcome of any pregnancy is guaranteed. The first criterion of therapeutic uniqueness is essential; without it, there is no rationale for the marketing of potentially teratogenic drugs.

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